

SUPPLEMENTARY MATERIAL

Assessment of Ibrutinib Scheduling on Leukocyte, Lymph Node Size and Blood Pressure Dynamics in Chronic Lymphocytic Leukemia through Pharmacokinetic-Pharmacodynamic Models

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Nlmixr model code

PK-SPD-leukocyte model

```
run100 <- function() {  
  desc = "pop PKPD, leukocytes and tumor size measurments"  
  est = "focei"  
  control = list()  
  ini({  
    # PD leukocytes $THETA  
    tcbldbas    <- fix(4.1644135)      # 10^9 cells  
    tclnbas    <- fix(7.6449086)      # 10^9 cells  
    tbldnrm_tn  <- fix(3.4941826)      # 10^9 cells  
    tbldnrm_rr  <- fix(2.8503700)      # 10^9 cells  
    tkdb1       <- fix(-4.8761701)      # day-1  
    tkh        <- fix(-0.7571987)      # day-1  
  
    # PD Tumor size (SPD) $THETA  
    tspdbas_unm  <- fix(3.8860955)      # cm2  
    tspdbas_m    <- fix(2.9725082)      # cm2  
    tlnss       <- fix(0.7843116)      # cm2  
    tkdt1       <- fix(-1.7320378)      # day-1  
    tkp1        <- fix(-5.4811627)      # day-1  
    tsip2       <- fix(2.4260423)      # unitless  
    tsip3       <- fix(-2.3192759)      # unitless  
    poplogit_fr1 <- fix(-0.1152389)      # unitless
```

```

poplogit_fr2 <- fix(-1.3357462)    # unitless

# PD combined $THETA

tic50      <- fix(3.5299932)  # hr.ng/ml
tkout      <- fix(0.2986911)  # day-1

tlmbd      <- fix(-7.0012733)  # day-1

lambda1    <- fix(-0.1931613)      # unitless

# $OMEGA (variances)
eta.cblbas ~ fix(3.986072)
eta.clnbas ~ fix(0.2703597)
eta.bldnrm ~ fix(0.3730409)
eta.kdb1   ~ fix(0.6146217)
eta.kh     ~ fix(1.67375)
eta.spdbas + eta.lnss ~ c(fix(1.0127872),
                           fix(0.5053674), fix(0.6420107))

eta.kdt1   ~ fix(1.572316)
eta.kp1    ~ fix(0.5444774)
eta.frc1   ~ fix(1.286532)
eta.frc2   ~ fix(1.41655)
eta.ic50   ~ fix(2.281496)
eta.kout   ~ fix(2.190465)
eta.lmbd   ~ fix(0.8146673)

```

```

# $SIGMA (sd)

add.sd1 <- fix(0.2043994)
add.sd2 <- fix(0.2208791)

})

model({


# PD parameters

etacblbasbox <- ((exp(eta.cblbas)^lambda1)-1)/lambda1
cblbas      <- exp(tcblbas + etacblbasbox)
clnbas      <- exp(tclnbas + eta.clnbas)
bldnrm_tn   <- exp(tbldnrm_tn + eta.bldnrm)
bldnrm_rr   <- exp(tbldnrm_rr + eta.bldnrm)
kdb1        <- exp(tkdb1 + eta.kdb1)
kh          <- exp(tkh + eta.kh)

etaspdbasbox <- ((exp(eta.spdbas)^lambda1)-1)/lambda1
spdbas_unm  <- exp(tspdbas_unm + etaspdbasbox)
spdbas_m    <- exp(tspdbas_m + etaspdbasbox)
lnss        <- exp(tlnss + eta.lnss)
kdt1        <- exp(tkdt1 + eta.kdt1)
kp1          <- exp(tkp1 + eta.kp1)
slp2        <- exp(tslp2)
slp3        <- exp(tslp3)

```

```

ic50      <- exp(tic50 + eta.ic50)
kout      <- exp(tkout + eta.kout)

lmbd     <- exp(tlmbd + eta.lmbd)

logit_fr1 <- exp(poplogit_fr1 + eta.frc1)
frc1      <- logit_fr1/(1+logit_fr1)
logit_fr2 <- exp(poplogit_fr2 + eta.frc2)
frc2      <- logit_fr2/(1+logit_fr2)

igvh    <- IMPIGVHMS # predefined variables in the dataset
iarm    <- TRTARM
auc     <- DAILYAUC

#####
# define variables #
#####

bldnrm  = bldnrm_tn*(1-iarm) + bldnrm_rr*(iarm)
spdbas  = spdbas_unm*(1-igvh) + spdbas_m*(igvh)

base_btk = 1
kin     = kout*base_btk

effauc = (auc/(ic50 + auc))           # pbtk inhibition by ibrutinib

resist  = exp(-lmbd*t)                # resistance development

slp1    = 1

```

```

krdt    = kp1
kp2    = kp1

effauc1 = slp1*resist*(1-btk)    # ibrutinib effect on proliferation
effauc2 = kdt1*resist*(1-btk)    # death in lymphoid tissues by ibrutinib
effauc3 = slp1*(1-btk)          # ibrutinib effect on homing from blood to tissues
effauc4 = slp2*(1-btk)          # ibrutinib effect on release of CLL cells (colony 1) from
stroma to surrounding tissues
effauc5 = slp3*(1-btk)          # ibrutinib effect on release of CLL cells (colony 2) from
stroma to surrounding tissues

# Scaling Factor
sc1    = clnbas/spdbas
sc2    = spdbas/clnbas

kht    = kh*sc2*bld_tcll
crdlnbas = frc2*clnbas
krd    = (kh+kdb1)*(cbldbas/crdlnbas)
krdcell = krd*sc1*ln_spd

#####
# define PD DV variables #
#####

wbc_bld = (bld_tcll + bldnrm)/5                      # leukocytes (10^9/L), bld vol = 5L
tot_spd = ln_spd + rln_spd + rln_spdq + lnss         # spd (cm2)

```

```

#####
# init cmt #
#####

btk (0)      = base_btk

rln_spd (0)  = spdbas*(1-frc2)*(1-frc1)
rln_spdq (0) = spdbas*(1-frc2)*(frc1)
ln_spd (0)   = spdbas*(frc2)

bld_tcll (0) = cbldbas

###

#####
# ODEs #
#####

d/dt(btk)      = kin* (1- effauc) - kout*btk

d/dt(rln_spd)  = kp1* (1- effauc1)* rln_spd - krdt* (1+ effauc4)* rln_spd
d/dt(rln_spdq) = kp1* (1- effauc1)* rln_spdq - krdt* (1+ effauc5)* rln_spdq
d/dt(ln_spd)   = kp2* (1- effauc1)* ln_spd + krdt* (1+ effauc4)* rln_spd + krdf* (1+ effauc5)*
rln_spdq + kht* (1- effauc3) - (krd + effauc2)* ln_spd

d/dt(bld_tcll) = krdcell - kh* (1- effauc3)* bld_tcll - kdb1* bld_tcll

```

```

ln_spd_ipred = log(tot_spd + 1E-6)      # spd (cm2)
wbc_bld_ipred = log(wbc_bld + 1E-6)      # leukocytes (10^9/L)

ln_spd_ipred ~ add(add.sd1) | SPD
wbc_bld_ipred ~ add(add.sd2) | LEUK

})

}

```

PK - blood pressure model

```

run200 <- function() {
  desc = "pop PKPD, systolic BP measurments"
  est = "focei"
  ini({
    # PD systolic BP $THETA
    tsbpbas <- fix(4.83995310) # mmhg
    tmtt   <- fix(4.38126172) # days
    temax  <- fix(-2.17877709) # unitless
    tec50   <- fix(4.51798998) # hr.ng/ml
    eff_age_mtt <- fix(-5.03804114)

    # $OMEGA (variances)
    eta.sbpbas ~ fix(0.006833436)
    eta.mtt   ~ fix(0.9173332)
    eta.emax  ~ fix(0.239243)

    # $SIGMA (sd)
    add.sd1 <- fix(0.08438139)

  })
  model({
    # PD parameters
    sbpbas  <- exp(tsbpbas + eta.sbpbas)
    mtt     <- exp(tmtt + eta.mtt + eff_age_mtt*LNAGE)
    emax    <- exp(temax + eta.emax)
    ec50    <- exp(tec50)
  })
}

```

```

auc      <- DAILYAUC # predefined variable in the dataset

###


#####
# define variables #
#####

nn      = 2
koutbp = nn/mtt
kinbp   = sbpbas*koutbp
effauc  = (emax*auc)/(ec50 + auc)

###


#####
# init cmt #
#####

trans1(0) = sbpbas
sbp(0)    = sbpbas

###


#####
# ODEs #
#####

d/dt(trans1) = kinbp* (1+ effauc) - koutbp* trans1
d/dt(sbp)    = koutbp* trans1 - koutbp* sbp


sbp_ipred  = log(sbp + 1E-6)          # systolic blood pressure (mm Hg)
sbp_ipred ~ add(add.sd1)


})

run300 <- function() {
  desc = "pop PKPD, diastolic BP measurments"
  est = "focei"
  ini({

```

```

# PD diastolic BP $THETA
tdbpbas  <- fix(4.24388453)  # mmhg
tmtt    <- fix(5.08188777)  # day
temax    <- fix(-2.66779698) # unitless
tec50    <- fix(4.14476079)  # hr.ng/ml
eff_age_bas <- fix(-0.20429000)

# $OMEGA (variances)
eta.dbpbas ~ fix(0.008102388)
eta.emax  ~ fix(0.7615876)

# $SIGMA (sd)
add.sd1  <- fix(0.08883375)

})

model{

# PD parameters
dbpbas  <- exp(tdbpbas + eta.dbpbas + eff_age_bas*LNAGE)
mtt     <- exp(tmtt)
emax   <- exp(temax + eta.emax)
ec50    <- exp(tec50)

auc     <- DAILYAUC # predefined variable in the dataset

###

######
# define variables #
######

nn      = 2
koutbp = nn/mtt
kinbp   = dbpbas*koutbp
effauc  = (emax*auc)/(ec50 + auc)

###

######
# init cmt #
######

trans1 (0) = dbpbas
dbp (0)   = dbpbas

###

#####

```

```
# ODEs #
#####
d/dt(trans1) = kinbp* (1+ effauc) - koutbp* trans1
d/dt(dbp)   = koutbp* trans1 - koutbp* dbp

dbp_ipred  = log(dbp + 1E-6)      # diastolic blood pressure (mm Hg)
dbp_ipred ~ add(add.sd1)

})
```